CLINICAL ETHICS

How tall is too tall? On the ethics of oestrogen treatment for tall girls

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Oestrogen treatment for girls, to prevent psychosocial problems due to extreme tallness, has been available for almost 50 years but uncertainty about its position prevails. The ethical problems of this treatment are focused on in this paper. After a brief overview on historical and medical aspects, ethical issues such as the general justification of oestrogen treatment, evaluation of its success and ethical concerns related to research in this subject are dealt with in detail.

A 10-year-old girl is referred to a paediatric endocrinologist because of expected extreme tallness. Her predicted adult height is 188 cm. On the basis of her family history and normal clinical examination, she is considered to be constitutionally tall. Should she be offered pharmacological treatment to reduce her adult height?

In the following, I consider both the scientific and the ethical aspects of this issue. My analysis is based on the existing scientific literature and interviews of several Finnish paediatric endocrinologists.

BACKGROUND

Experiences in the treatment of acromegaly and observations among children with precocious puberty led to the first ideas of treating healthy tall girls with hormones to reduce their adult height.[1 2] The first scientific report of this treatment was published in 1956 by Goldzieher,[3] who described 14 girls who had been treated with oestrogen and testosterone or oestrogen only. The treatment was considered to be justified because extreme tallness was ''likely to raise social and economic problems''. The height indications were either 66 inches (167.6 cm) and full-growth potential (open epiphysial lines) or <66 inches but at least 4 inches above average. The average gain in height was 2 inches (range 0–6.25 inches). The treatment was generally well tolerated. In two cases, however, the breakthrough bleedings were excessive.[3]

The treatment has thus been available for almost 50 years. Despite much research, numerous scientific reports and the tens of thousands of girls treated, uncertainty about the position of oestrogen treatment prevails. Although no data exist on the exact numbers of girls treated, clearly, the promptness with which treatment is started varies greatly between countries, regions and individual physicians—for example, in Norway, it was possible to collect a series of 539 treated girls in 15 years (1970–85),[4] whereas in Finland, a country with only a slightly larger population, hardly one fifth as many girls were treated during the same period (J Perheentupa, personal communication, 2003). In Finland, a decreasing demand for oestrogen treatment has also been noted by paediatric endocrinologists who have worked in this area for several decades. Societies have probably become more tolerant with respect to tallness, shortness and other extremes of normal variation.

The principal aim of this treatment is, of course, to prevent anticipated psychosocial problems caused by extreme tallness in adulthood. In the literature, these problems are sometimes mentioned only in passing as ''likely'',[3] and at other times they are given thorough consideration. For example, Wettenhall *et al*[5] mentioned the following potential problems: feeling different, being subject to hurtful comments, withdrawal from social activities, difficulties in finding appropriate clothes and difficulties in finding a partner. The risk of remaining unmarried was hardly ever mentioned directly in the reports written in English, but a German review[6] frankly mentioned parents' worry that their daughter's unusual body size would compromise her chances of marrying. Interestingly, the same report also states that the girl herself is usually not worried about her size and may even be proud because she is often considered to be older than she actually is.

Predicting future psychological well-being is extremely difficult, whereas predicting adult height is less so. The methods for predicting adult height have developed considerably since the days of Goldzieher, but contrasting views have been expressed even as late as the 1990s. On the one hand, Ignatius *et al*[7] noted the poor accuracy of height predictions, particularly for extreme plus variants. On the other hand, Drop *et al*[2] wrote that ''height prediction in tall girls is quite accurate regardless of which method is used'' and that ''predicting adult height becomes more accurate with increasing age''. They admit, however, that ''considerable errors may be made in individual cases'' because of the relatively large SD of the mean errors of prediction.

The predicted adult height that has been suggested as a criterion for considering hormone treatment has varied from 177 cm (Australia, 1960s[5]) to 185 cm (Germany, 1980s[8]). The criteria, however, reflect the opinions of experts and are generally not nationwide. This variance is, of course, partly explained by the secular trend in growth. The mean height of Dutch army recruits, for example, was 178 cm in 1965 and 182 cm in 1980.[2] Not many data are available on girls, but a similar trend is obvious. Generally, often the height criterion has been expressed in centimetres (or inches in the earliest papers), but

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sometimes SD is used (eg, +2.5 SD, Norway, 1970s[4]). Occasionally, additional physical criteria, such as skoliosis, are considered.

The great variability in the number of girls treated is easily understandable in light of the following examples in which authors from different countries describe their criteria for considering treatment. At the other extreme, the criteria are simply based on centimetres. Schoen *et al*[9] recommended treatment if the expected adult height was 182.9 cm (72 inches) or more, and they offered treatment but did not strongly recommend it if the expected height was between 177.8 and 182.9 cm. Other authors emphasise the psychological or psychosocial indication in various ways. Prader *et al*[10] preferred hormone treatment ''only if there is really an urgent psychosocial indication'', Andersen *et al*[11] treated only ''girls with severe psychosocial problems due to excessive height prognosis'' and Panteon *et al*[12] considered treatment ''only when the psychological burden of being 'tall for a girl' cannot be ameliorated by other means of therapy''. According to Marshall,[13] consultation with a potentially tall girl leads to ''reassurance or, occasionally, treatment''.

ETHICAL ISSUES

Clearly, the ethical justification of any treatment for healthy people to prevent future psychological harm is a serious issue. To me, after having interviewed several paediatric endocrinologists, it is just as obvious that the values of the girl and her family are seriously considered in individual treatment decision. In the medical literature, however, the ethical questions have been dealt with only in passing, if at all. My aim here is to examine the general justification of this treatment, issues related to the evaluation of its success and ethical issues related to research in this area.

General justification

The harmfulness of tall stature in adulthood has usually been taken for granted in the medical literature. No evidence, however, has been presented to support this view. Both interviews and the literature show that the experiences of a tall mother are often the main reason why treatment is sought for a tall girl. For example, Bailey *et al*[14] note that ''the tall mother who has had an unhappy adolescence may be much more concerned about tall stature than her daughter''. One of the interviewees said, ''Sometimes I feel that any treatment is better than daily discussions at home about the harmfulness of tall stature.''

Authors differ in their opinions about the views of tall girls on possible treatment. On the one hand, expected excessive tall stature is seen as ''a severe physical and psychological burden for otherwise healthy adolescent girls''.[15] On the other hand, as noted earlier, a German author[6] also states that the girl herself is usually not worried about her size. According to one of my interviewees, it is common for the mother to be eager for her daughter to be treated, whereas the girl herself has no opinion and the father is an outsider.

Repeated investigations also serve a message to the girl. As one of my interviewees asked quite frankly, ''How do you deliver the message 'you're OK' between several visits to endocrinologists to consider height predictions and hormone treatments?''

The girls are healthy, but this is not always obvious even to the researchers working in this area. Weiman *et al*[16] mentioned that, in their study population, ''none of these girls suffered from any other disease'', and Peters *et al*[15] wrote about ''otherwise healthy adolescent girls''.

The treatment for tall girls is, of course, not unique in the sense that healthy children are treated to prevent future psychological harm. Human growth hormone treatment for constitutionally short children is one example. The US Food and Drug Administration has recently approved human growth hormone treatment for children who are more than 2.25 SD below the mean for age and sex, which means 1.2% of all children.[17] Another example from paediatrics is surgical reduction of big ears. The operation is simple, but complications can occur, as with any surgical procedure.

All these treatments show the limits of evidence-based medicine. It would be simply unethical to conduct a trial aimed at determining a value for number needed to treat for oestrogen treatment, for example, to prevent psychological harm due to extreme tallness.

In all of medicine, a decision to treat is, of course, always the result of facts and values being weighed. Sometimes the facts are so obvious that value judgements are simple (eg, insulin in the case of diabetes). At some other times, there may be evidence from randomised controlled trials with a placebo group, but the value considerations are complicated (eg, antibiotics in the case of otitis media). The treatment for tall girls represents the other extreme in that the treatment decision must consist of a careful weighing of available facts and the values of the girl, her family, the doctor and society.

The issue of consent is complicated, because the age at which the initiation of this treatment is useful (at least in terms of height) falls into a grey area between early childhood and maturity. It has been convincingly shown that the earlier the treatment is started, the greater is the effect.[2 7] On the basis of several studies, it has been estimated that the mean effect of oestrogen treatment on final height is 6 cm when the bone age is 10 years at the start of the treatment, 2 cm at 13 years and 0 at 14 years.[2] In addition, some side effects, such as psychological stress due to early menstruation and interest in the opposite sex, are especially clear among the youngest.[7]

Thus, at an age at which a girl is able to give her valid informed consent, she no longer benefits from treatment. The ability to consent to treatment, however, should not be understood dichotomically. Younger girls should also take part in the decision-making process along with their parents. In practice, their refusal of treatment is respected.

When is treatment successful?

Is it possible to know whether the treatment has been successful in a particular case? The answer is simply no if the primary aim, future psychosocial well-being, is considered. On the other hand, if its surrogate, final height, is considered, then one way to measure success is to compare the actual height with the predicted height. Even then it is not at all obvious, however, what would constitute a ''good'' result.

Although it is not possible to determine the success of this treatment in individual cases, some attempts have been made to evaluate it at the group level. Although randomised controlled trials have not been conducted, which is understandable in view of the methodological and ethical considerations, questionnaire studies to assess patient satisfaction have been conducted retrospectively.

According to a study by Weiman *et al*,[16] 84.6% of the treated girls are grateful for having been treated and 15.4% regretted it. In addition, 38.4% recalled the side effects of treatment as unpleasant, whereas 61.5% did not. Ignatius *et al*[7] also asked the girls retrospectively about their satisfaction with the decision regarding the treatment. Altogether, 80% of those treated and 64% of those not treated were happy with their decision. Moreover, the girls were asked their opinion of their final height. Interestingly, 82% of those treated and 79% of those not treated were satisfied with their final height.

Research ethics

Although randomised placebo-controlled trials have not been conducted on oestrogen treatment, other research activity has been high. The conclusion of a symposium in 1978 was that it is ''urgent that studies be done to evaluate the psychological

benefit of treatment vs. no treatment''.[18] In the world of evidence-based medicine, this would mean a randomised trial with a decades-long follow-up. One arm of the trial would be the treatment group and the other either a placebo group or a non-treatment group with similar follow-up. Although such a trial would have a scientific rationale, clearly neither paediatric endocrinologists nor tall girls or their families would give their consent. After all, the evidence for the final height-reducing effect of the treatment may be strong, but evidence of its effect on psychological well-being is missing.

The third possibility is a randomised trial in which one arm of the trial would receive hormone treatment and the other arm would undergo psychotherapy or counselling. This kind of setting would seem to be scientifically sound, but, again, it is probably not feasible in practice.

Thus, we seem to be in a situation where, on the one hand, we have a great deal of information on all the biological aspects of the treatment (dosages, mechanisms, effects, short-term side effects) and even more is accumulating; and on the other, we still do not know—and probably will never know—whether the treatment is effective in terms of the main goal, future psychosocial well-being.

Randomised controlled trials, however, are not the only sources of reliable evidence in medicine. For ethical or methodological reasons, they are often impossible to conduct. Carefully planned alternative study designs can be helpful too. A step forward could be the requirement that these girls were treated and followed up only within studies in which adequate evaluations are built in.

The issue of informed consent does not have unique features when compared with other research among children of the same age. Two studies, however, report the differences in the consent process. I mentioned earlier the Norwegian study on 539 girls.[4] What is troubling from the point of view of informed consent is that of the 539 girls and families to whom the treatment was offered, all accepted. This result raises a question about the directiveness of the researchers who offered the families and the girls the first information about the study. In the same year, a much smaller Finnish study of 87 girls was published. In this case, 59 girls accepted and 28 rejected treatment.[7] The patient information was probably more neutral in the Finnish study.

Although randomised trials with a placebo, non-treatment or counselling group will perhaps never be conducted with oestrogen treatment for tall girls, there are certain issues that can and should be considered in other kinds of clinical research settings. The follow-up of these girls has not been long enough to assess long-term side effects such as breast cancer, and the series has been too small for reliable estimates of side effects in general.

Some methodological issues, however, make research on the long-term side effects difficult. Firstly, reliable nationwide cancer registers exist only in a few regions of the world. The Nordic countries have such registers, but adequate study size would require international cooperation, and whether current data protection legislation would permit such research is still an open question.

Reliable estimates of short-term side effects would also require rigid study protocols and large sample sizes. Because the problem is not common and owing to the social trend towards tallness being better tolerated, to acquire a sufficiently large study sample would, again, require international cooperation. Such cooperation, in turn, may prove difficult because of different traditions in clinical practice. In addition, the highly individualised nature of treatment decisions may make the creation of strict inclusion criteria difficult.

Alternatives to oestrogen treatment, such as bromocriptine and somatostatin analogues, have been studied to some extent.[2] Because of the potential long-term side effects of oestrogen, new drugs would be welcome, but, again, ethical obstacles may hamper the research that would be necessary. The participants of a possible randomised trial comparing standard treatment with treatment using a new drug would have to be informed that, with high probability, the standard treatment would reduce the final adult height, but that the same cannot be said about treatment with the new drug.

CONCLUDING REMARKS

For decades, girls have been receiving oestrogen treatment to prevent extreme tallness, but uncertainty about its position prevails. Several reasons may explain why the situation is still unclear. It is impossible to estimate the success of the treatment in individual cases. At the group level, it would be possible, in principle, but a placebo-controlled trial would hardly be ethically justified.

Despite all the research that has been conducted, many uncertainties are still linked to oestrogen treatment for tallness. Because the problem is unique in each case, it will never be possible to determine the criteria for treatment in the same sense as in, for example, clinical practice guidelines for high blood pressure. Much is known about the short-term side effects, but their true frequency remains unknown. Much less is known about the long-term side effects, and research on this topic would be particularly important.

As in the case of human growth hormone treatment for constitutionally short children or surgery for children with big ears, pharmacological treatment to prevent psychosocial harm among healthy tall girls is, in a way, treating the victims of the attitudes of families and society. This observation, however, does not help the girls. Although society may have become more tolerant, pharmacological intervention may sometimes be appropriate.

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